

REVIEW ARTICLE

Depression, a major comorbidity of psoriatic disease, is caused by metabolic inflammation

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Abstract

Psoriatic disease is a chronic, systemic immune-mediated inflammatory disorder comprising three major domains, skin, vascular and bone/joint inflammation. It is known for a long time that psoriatic disease is associated with a number of conditions such as hypertension, dyslipidemia, diabetes (metabolic syndrome) and depression. Up to one out of five people with psoriasis show concomitant depression. In the past, this was attributed to psychological stress of suffering from a chronic condition that is often visible and itchy, leading to stigmatization and adding to a significant burden of disease. Recent data provide evidence that depression associated with psoriatic disease is linked to the specific inflammatory pattern with IL-23, IL-17 family cytokines, TNF, IL-6 and IL-8 causing neuroinflammation and subsequently depression or depressive behaviour and/or anxiety. Psoriatic disease shows a distinct pattern of immune cells (e.g. dendritic cells, Th17 cells, neutrophils), mediators (e.g. IL-17A/F, IL-23, TNF) and tissue-related factors in all major domains that is different from other inflammatory dermatoses. There is a striking similarity between the inflammatory pattern in psoriatic disease and neuroinflammation that leads to depression. A number of risk factors have been identified in psoriatic disease, the most important of which are obesity and tobacco smoking. Obesity is known as a major risk factor for depression and anxiety due to its inflammatory signature. Apart from psychotherapy and anti-depressive medication, targeted treatments for psoriasis, including TNF, IL-17 and IL-23 inhibitors, can improve depression/depressive symptoms. The review summarizes the current knowledge about depression as a comorbidity in psoriatic disease.

INTRODUCTION

Psoriatic disease is a complex immune-mediated chronic inflammatory condition for which there is no cure. The disease has at least three major domains, all characterized by a similar pattern of inflammation. Skin inflammation usually is the first manifestation leading to the diagnosis. In a small number of people, symptomatic joint involvement can precede skin lesions. Studies, mainly performed by cardiologists, have shown that psoriatic disease is linked to generalized vascular inflammation not only of small but also of large vessels.¹

Apart from these major domains, psoriatic disease is associated with a number of concomitant conditions referred

to as comorbidity. Hypertension, atherosclerosis, diabetes mellitus type II/insulin resistance, dyslipidemia and the related metabolic syndrome are well documented in psoriatic disease. In addition, a wide range of other conditions has been described to be associated, including sleep apnea, non-alcoholic steatosis hepatitis (NASH) and uveitis. In the last years, depression has been recognized to be comorbidity, but its relevance was underestimated because of sparse data.

Psoriatic disease can be strongly influenced by risk and trigger factors. Among them, obesity is by far the most important risk factor and smoking adds to this scenario. A range of trigger factors is known to cause a first disease onset or flares during the disease course. Stress is

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highlighted by people suffering from psoriatic disease as the most frequent and important trigger factor, followed by infections such as tonsillitis and periodontitis.² Drug triggers play only a minor role in this context. In Figure 1, the important spheres of psoriatic disease are shown.

THE PATTERN OF PSORIATIC INFLAMMATION

In the last years, the pathophysiology of the inflammation pattern in the skin has been thoroughly characterized. Two major components were identified as being responsible for a core inflammatory pathway: dendritic cells producing and secreting interleukin-(IL)-23 and activated T cells of a Th17 phenotype-producing IL-17 cytokines.³ A range of bystander cytokines participate in the inflammatory scenario with varying importance for phenotypic subtypes of the psoriatic disease spectrum. These include TNF, IL-6, IL-36, and interferon γ .

A hallmark of the inflammatory pattern in psoriatic disease is the presence of neutrophils, a prominent member of innate immunity. In plaque psoriasis neutrophils actively immigrate from the microvasculature into the skin and aggregate in the stratum corneum to form microabscesses. When activated and forming neutrophil extracellular traps (NETs), their histone content can promote the generation of Th17 cells and induce IL-17 secretion, which enhances IL-17-type inflammation.⁴ Free RNA of NETs can stimulate plasmacytoid dendritic cells after complexing with the antimicrobial protein LL-37, resulting in the production of IL-8, a prominent chemotaxin for neutrophils, and TNF and IL-6 generating an inflammation-promoting loop.⁵

Very recently, it has been shown that neutrophils home at the enthesis in early enthesitis and upon stimulation produce/secrete IL-23.⁶

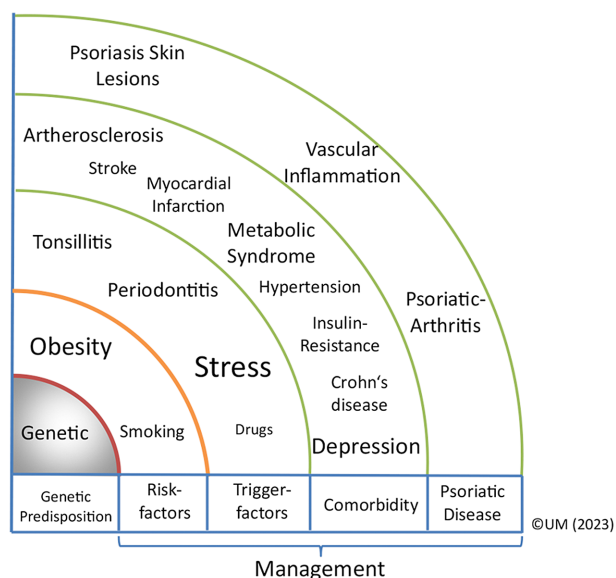


FIGURE 1 Spheres of psoriatic disease.

Regarding the third domain of psoriatic disease, vascular inflammation, there is an increased expression of genes related to neutrophil degranulation in the transcriptome of the blood of people with psoriasis with cardiovascular disease (CVD) compared with people with psoriasis without CVD. A higher neutrophil-lymphocyte ratio (NLR) may serve as a marker of subclinical CVD in psoriasis.⁷

The IL-23-IL-17 axis is also involved in bone/joint and vascular inflammation. In the very early event of enthesitis involvement, not yet leading to clinical symptoms, the inflammatory signature is similar to the one in the skin. Here, IL-17 cytokines in particular IL-17F are driving inflammation. TNF, together with IL-6, are the most important bystander cytokines in psoriatic inflammation in all three major domains. In psoriatic disease, TNF is a known therapeutic target.

Research, mainly from cardiology, showed the generation of non-calcified atherosclerotic plaques very early after the onset of the disease, and it can be hypothesized that vascular inflammation is already present by the time psoriasis is diagnosed. IL-17 cytokines dominate the specific inflammation in the vessel wall or in the surrounding perivascular fat, for example the coronary arteries.¹ IL-6 and TNF have been described to be part of the spectrum together with IL-1. It is of note that the IL-1 antagonist canakinumab was able to improve atherosclerotic disease⁸ but is ineffective in treating plaque psoriasis.

COMORBIDITY IN PSORIATIC DISEASE

Since 1995, it is known that psoriasis is associated with other conditions on the basis of disease concomitance.⁹ Among the most prevalent non-cutaneous diseases, hypertension, heart failure and diabetes are known. Since this first description, many other conditions have been found in association with psoriatic disease (Table 1). Among these, dyslipidemia and depression became important as they are closely linked to inflammation but also to consequences of comorbidity such as mortality. The cardio-metabolic consequences of psoriatic disease are well established.¹⁰ In a retrospective study, using the database of a large US healthcare insurance, it was found that the risk for myocardial infarction was significantly increased in people with psoriasis.¹¹ In people <60 years of age dyslipidemia increased this risk by 7.4-fold followed by hypertension (3.2-fold). In people >60 years of age, hypertension was the most prominent risk factor (HR 25.1), followed by dyslipidemia (HR 5.9). Consequently, it was shown that statin treatment highly significantly reduced the risk of myocardial infarction in both age groups and may reduce endothelial dysfunction.¹²

In a recent experimental study, an increase of Th17 cells and a reduction of CD69+ regulatory T cells (T reg) were demonstrated in people with metabolic dysfunction showing dyslipidemia and insulin resistance.¹³ The number of

TABLE 1 Comorbidity in psoriatic disease.

Hypertension
Dyslipidemia
Diabetes mellitus type 2
Atherosclerosis/CVD
Depression
Anxiety
NASH
Sleep apnea
Vitiligo
Osteoporosis
Bullous pemphigoid
Crohn's disease
Renal disease
Gout/hyperuricemia

pathogenic Th17 cells was mainly increased in people that were also overweight.

THE IMPORTANCE OF STRESS AND/OR STRESSFUL LIFE EVENTS FOR PSORIASIS

In a recent project to define activity types of psoriasis (ActiPso), people with psoriasis were asked if their personal psoriasis can be triggered by events.² Of those reporting psoriasis flares due to triggers, more than 90% named stress as the triggering event. People having an unstable disease course or of the winter-type report more about the influence of trigger factors than people with stable psoriasis.

In a small, prospective study comparing people with psoriasis to healthy controls, it was concluded that chronic psychosocial stressors like childhood maltreatment may predispose to the manifestation of psoriasis.¹⁴ The link between stress and psoriasis was substantiated by an investigation of soldiers of the US army after deployment in Afghanistan.¹⁵ Those returning with post-traumatic stress disorder were most likely to develop either rheumatoid arthritis or psoriasis in the post-stress period. A genetic pleiotropy was discussed as the reason for this observation.

There are numerous pathways by which stress can modulate inflammatory immune responses of importance for the pattern in psoriasis. In a recent survey, the role of mast cells was discussed as a mediator between stress events, innate immune system activation and signature cytokines of relevance for psoriasis.¹⁶ Mast cell activation together with endothelial cell swelling was shown as the earliest sign in relapsing psoriasis skin lesions.¹⁷ In addition, skin mast cells are a major source of IL-17 that can be released immediately after activation/degranulation.¹⁸ IL-17-positive mast cells are increased in lesional psoriasis skin and, together with IL-17-positive neutrophils, in the joints of people with spondyloarthropathies.¹⁹

Stress can aggravate hypertension by activation of dendritic cells through oxidative stress and the generation of IL-1, IL-6 and IL-17.²⁰ In a study with 164 people with psoriasis and 47 healthy controls activation of the amygdala was found in people with psoriasis, leading to increased bone marrow activity, releasing immune cells that contribute to subclinical vascular inflammation.²¹ There is a correlation between psoriasis duration and vascular inflammation and major adverse cardiovascular events (MACE), suggesting that chronic exposure to low-grade chronic inflammation can contribute to vascular disease development and MACEs.²²

RISK FACTORS FOR PSORIASIS

Genetics

A positive family history is a risk factor for psoriasis. Genetic studies performed over the last decades have identified more than 87 genetic susceptibility loci, with HLA C*06 being the most important.²³ None of these loci alone or in combination are necessary to suffer from severe psoriasis. In psoriatic arthritis, HLA B27 is particularly found in subgroups of patients with predominantly axial involvement, distinct from axial spondylitis.

Smoking

In the Danish National Birth Cohort study, investigating 25,812 children, it was found that prenatal smoking increased the risk for psoriasis by 1.47-fold, smoking of the mother/father in the first year after birth by 1.49-fold and during childhood by 1.37.²⁴ In pregnant women who smoked more than 16 cigarettes/day, the risk for the child to develop psoriasis was increased by 2.96. In a systematic review, the risk to develop psoriasis in ever smokers was increased by 1.84-fold.²⁴ However, data on the effect of non-smoking in former smokers on a population basis do not exist.

It is known that tobacco smoking activates inflammatory immune pathways in psoriasis.²⁵ In humans an increase in inflammatory CD4⁺ Th17 lymphocytes in blood and lung tissue is present in smokers.²⁶ Tobacco smoke extract promoted Th17 generation from memory T cells in vitro and increased expression of IL-17 and IL-22.²⁷ Experimental evidence demonstrates that CCR6⁺ Th17 cells showed a higher sensitivity to cigarette smoke extract-induced oxidative stress and higher VEGF α secretion. This contributes to pro-angiogenic and pathogenic CCR6⁺Th17 cells. Induction of Th17-pathways has also been shown in palmoplantar pustulosis.²⁸

Apart from activating adaptive immunity responses, tobacco smoke-derived benzo(a)pyrene activated arylhydrocarbon-receptor (AhR)-inducible pathways. AhR activation lead to increased IL-8 expression in a CYP1A1-dependent manner.²⁹ IL-8 is the major chemokine for driving neutrophils into the epidermis in psoriasis skin lesions.

Obesity

The most important risk factor for psoriatic disease is obesity. On a population basis, the strongest evidence for obesity being crucial for psoriatic disease comes from studies performed in Denmark and Sweden. In the Swedish Obese Subjects study, 1991 subjects who underwent bariatric surgery and 2018 obese controls, all without psoriasis, were followed up for up to 26 years.³⁰ Mean body mass index (BMI) was 40 in the control and 42 in the surgery group. In the surgery group, the adjusted hazard ratio (HR) for psoriasis was 0.65, indicating a 45% reduction in the risk of developing psoriasis. Smoking and a longer duration of obesity were negatively associated with this risk reduction. In a Danish study, 12,364 people without psoriasis underwent gastric bypass surgery and were followed up for 10 years.³¹ The adjusted HR of psoriasis was 0.52, corresponding to a risk reduction of 48%.

Similar data were observed earlier in a case-control study in people with psoriasis.³² A two-fold risk for psoriasis was found in people with a BMI of >30.

Obesity is a known risk factor for all conditions associated with psoriatic disease including hypertension, diabetes mellitus/insulin resistance, dyslipidemia, atherosclerosis and depression (Figure 2).

Other risk factors for psoriatic disease

Patients with psoriasis often report about flares after alcohol intake, however, not on a limited regular basis but after excessive drinking events. In a recent study using a large database strategy, it was found that smoking, as described above, is a significant risk factor for psoriasis, but alcohol consumption, in general, is not.³³

Dietary factors have been discussed extensively regarding their potential as risk factors for psoriasis. Apart from general recommendations to favour 'healthy food' and to stay lean that there is no conclusive data about significant dietary

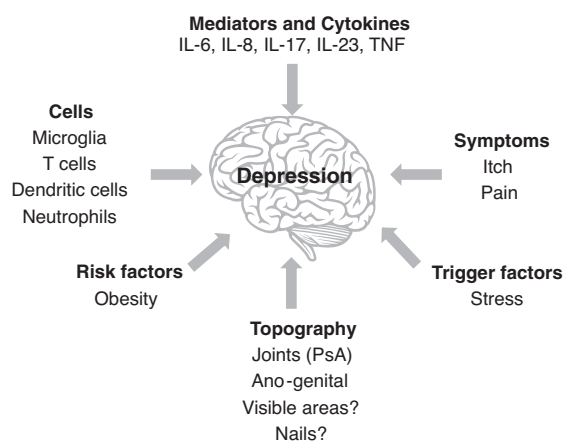


FIGURE 2 The complex scenario of metabolic depression in psoriatic disease.

risk factors across all ethnic groups. Gluten sensitivity was detected as a risk factor in some psoriasis phenotypes including palmoplantar pustulosis in patients with celiac disease as comorbidity, but there is no evidence for gluten being a risk factor in general.^{34,35}

Depression in psoriatic disease

Two decades ago, it was believed that stress associated with the presence of skin symptoms in psoriasis causes depression,³⁶ but it was also stated that depression is frequently found in people with psoriasis. Depression was seen as a consequence of the disease, but not as part of the disease itself.

The prevalence of depression is estimated to be at up to 20% of people with psoriasis in Western countries. In a population study in a central region of Sweden, 4587 people with psoriasis and 268,949 non-psoriasis controls were investigated. The diagnosis of depression was substantiated by ICD-10 coding and the related prescription of an antidepressant medication.³⁷ The rate of depression was significantly higher in the psoriasis group (16.9% vs. 11.0%) compared to the control population. The highest rate was found in females with psoriasis (21.1% vs. 12.6%). In this population, younger age was associated with an increased frequency of depression compared to the older age group. In addition, in psoriatic arthritis (PsA), there is an increased prevalence of depression and anxiety not only due to pain and physical disability but also due to a higher level of inflammation.³⁸ Symptoms of psoriasis such as itch and anogenital involvement add to depression and anxiety, particularly when they are moderate to severe.³⁹ Moderate to severe itch had a strong effect on depression and stigmatization and was associated with a reduced benefit from treatment, further adding to the severity of depression.

Only very recently, it was found that depression can be regarded as an inflammatory condition and the pattern of inflammation has striking similarities to that of psoriatic disease. In a study, it was highlighted that cognitive impairment is increased in people with chronic inflammatory diseases such as psoriasis.⁴⁰ This type of chronic low-grade inflammation may lead to 'inflammaging', particularly in the elderly.

Pathophysiology of depression in psoriasis

In an animal model of stress-induced depressive behaviour, the brains of mice were investigated and the inflammatory pathways were analysed.⁴¹ It was found that microglial activation led to a pattern of T-cell priming towards a Th17-type, with IL-17 being a main cytokine together with IL-6, and a reduction of Treg was seen. When depressed mice were treated with an IL-17A-inhibitor, a re-balancing of the inflammation pattern was seen, with IL-10 being upregulated and Treg numbers increased. In parallel, depressive behaviour was

changed to a normal behavioural state. In people with PsA, serum IL-23 levels correlated with depression and anxiety as well as PsA disease activity in a cohort study.⁴²

Numerous studies have shown that neuroinflammation is the backbone of depressive behaviour and depression. Independent of psoriasis, the pattern is IL-17- and IL-6-dominated and involves innate (microglia) and adaptive (T cells) immune cells/tissue. Cytokines present in the microvasculature may be able to penetrate the blood–brain barrier to act together with those generated in the micro-environment of neuroinflammation. It is therefore that depression, at least to a major extent, is regarded as an inflammatory condition.

The kynurenine pathway is involved in the interaction between immune responses and serotonin neurotransmission.⁴³ Inflammatory cytokines can activate the enzyme indoleamine 2,3 dioxygenase (IDO), which converts tryptophan into kynurenine resulting in a partial depletion of serotonin in the brain. An inflammatory environment with IDO shifts kynurenine metabolism towards microglial by-products such as 3-hydroxykynurenine and quinolinic acid, resulting in elevated oxidative stress and glutamate, which contributes to depressive symptoms.

In a recent study, major depressive disorder was linked to a neutrophil-related gene network in the peripheral blood.⁴⁴ This is of particular interest as neutrophils are hallmark cells of psoriasis. In this analysis, expression of IL-17RA and IL-23A was found, which is in line with the importance of these cytokines in other experimental models.

Neutrophils have been shown to be a key player in depressive disorders. Like in psoriatic disease, the neutrophil-to-lymphocyte ratio (NLR) is significantly higher in people with depression compared to healthy controls, according to a recent meta-analysis of 18 studies including more than 2200 patients and 2400 controls.⁴⁵ Due to their activation profile, neutrophils may modulate inflammatory responses, leading to an inflammation pattern unique for psoriatic disease and associated comorbidity including depression.⁴⁶

The latest data come from brain structural studies comparing people with psoriasis and depression with respective controls. In an investigation using data from the UK biobank and MRI imaging, it was found that thickness in the right precuneus was increased in people with psoriasis compared to controls only when depression was present.⁴⁷ In another cohort of 29 people with psoriasis and depression and 24 healthy controls, functional magnetic resonance imaging scanning was performed in addition to severity measures of psoriasis (PASI) and a self-assessment of depression (SDS).⁴⁸ In comparison to healthy controls, people with psoriasis and depression demonstrated an increased fractional amplitude of low-frequency fluctuation in the left frontal middle brain area (Frontal_Mid_L) and increased functional connectivity between the right hypothalamus region and the right middle cingulum (Cingulum_Mid_R). There was a positive correlation between PASI and SDS in people with psoriasis with depression, while functional connectivity was negatively correlated with SDS and PASI.

It is of note that other inflammatory skin disorders such as atopic dermatitis (AD) show an increased rate of associated depression, however, the inflammatory pattern leading to AD-related depression is different from that in psoriatic disease.⁴⁹

Risk factors for depression in psoriasis

The most important risk factor for psoriatic disease is obesity. As mentioned before, the risk of obese people to develop psoriasis is nearly double in comparison to weight loss states after bariatric surgery. In obese people, substantial inflammation is generated in the fatty tissue, predominantly in the central adipose tissue, which can be assessed apart from BMI by measuring the hip circumference or the waist-to-hip ratio (WHR). There is a striking correlation of many disorders with both, BMI and WHR.

When lean people become obese, one of the first signs is the active migration of inflammatory-type macrophages into the fatty tissue, which is mainly mediated by the cytokine monocyte-chemotactic peptide 1 (MCP-1). These macrophages interact with adipocytes in the microenvironment, resulting in the increased production of pro-inflammatory cytokines such as IL-6 and TNF and adipokines including leptin and resistin. These mediators are released into the peripheral bloodstream and disseminated throughout the body. As a consequence, obesity results in a pro-inflammatory state that is able to aggravate other inflammatory diseases, particularly those with a similar inflammatory pattern.⁵⁰ IL-8, a prominent chemotaxin for neutrophils, was found to be increased together with TNF and macrophage inflammatory protein (MIP)-1 β in people with major depressive disorder and obesity.⁵¹

Obesity is a known risk factor for depression, independent of other inflammatory diseases such as psoriasis. This notion has extensive implications for affected people entering a depression–obesity–inflammation cycle.⁵² Depression-dependent inactivity and dietary failures result in increased obesity, increasing inflammation and provoking other obesity-related conditions in a vicious cycle.

Treatment of depression related to psoriasis

The common pathway to treat clinical depression is linked to a proper diagnosis and consists mainly of psychotherapy and/or the use of anti-depressants. In psoriatic disease, depression occurs in the context of metabolic inflammation, and therefore, an alternative strategy is the use of drugs for psoriasis that improve inflammation and thereby improve depression. In a large analysis of immune-mediated inflammatory diseases (IMID), the effect of drugs on depressive symptoms was assessed.⁵³ The best effect on depressive symptoms was consistently seen with IL-6 antagonists used to treat rheumatoid arthritis, followed by the IL-12/-23 antagonist ustekinumab for psoriasis. Anti-TNF- and

anti-CD20-drugs showed a positive but less pronounced effect.

Signature cytokines as treatment targets

Treatments targeting dominant cytokines of psoriatic inflammation show efficacy and sustainability of clinical responses and an effect on all domains of psoriatic disease. The highest clinical efficacy with a fast onset of response can be achieved with IL-17 inhibitors, particularly with the IL-17 receptor antagonist brodalumab⁵⁴ and the IL-17A and F antibody bimekizumab⁵⁵ followed by IL-23 antagonists.⁵⁶ The longest time to remain disease-free after cessation of treatment or randomized withdrawal scenarios in clinical trials is seen with IL-23 antagonists.⁵⁷

Other treatments including TNF inhibitors or compounds with a broad spectrum of mechanisms of action including apremilast, ciclosporin or methotrexate are unable to provide this grade of efficacy and sustainability. It is of note that drugs targeting IL-6 have not been developed for psoriasis or psoriatic arthritis due to limited efficacy and the potential to induce paradoxical psoriasiform eruptions.^{55,58}

These data are supplemented by results from large clinical trial programs. For risankizumab, an IL-23p19 inhibitor, a significant improvement of hospital anxiety and depression scale (HADS) was shown through week 52 with measurable improvement as early as week 16 and superiority to ustekinumab.⁵⁹ Similar data were obtained for guselkumab,⁶⁰ another IL-23p19 inhibitor. In a comparative trial, guselkumab was superior to the TNF-antagonist adalimumab.⁶¹ Secukinumab and ixekizumab, anti-IL-17A antibodies, were shown to improve HADS-evaluated depression.^{62,63} Conclusive data on conventional drugs to treat psoriasis such as methotrexate, ciclosporin or fumarates are lacking. Acitretin, a retinoid, the phosphodiesterase 4-inhibitor apremilast and the IL-17RA-antagonist brodalumab were associated with depressive symptoms during their clinical development program and may only be used in people with psoriasis with known depression after consulting the treating psychiatrist/psychologist.

Impact of re-thinking depression in psoriatic disease for affected people

Until recently, depression in psoriasis was regarded as a psychological consequence of suffering from a chronic, visible illness, experiencing stigmatizing behaviour, social isolation and limited efficacy of treatments. As depression itself causes stigmatization, this leads to a vicious cycle.

Considering that depression is an inflammatory condition with neuroinflammatory events with a similar signature as in the major domains of psoriatic disease, people with psoriasis-associated depression are no longer responsible for their perceived lack of coping with psychological threads. This takes the burden from individuals and attributes

depression to the spectrum of conditions directly linked to psoriatic disease.

In the practical management of people with psoriatic disease, screening for depression by using simple clinical questions or respective tools needs to be implemented. As a screening tool, the 'two-question test' is an easy-to-use method.⁶⁴ Established tools such as the HADS or Beck's depression inventory (BDI) can subsequently be used to further substantiate the suspected diagnosis of depression. When considering drug treatment, those compounds with a documented effect on depression should be preferred.

AUTHOR CONTRIBUTION

UM drafted the manuscript and the figures and MS and SG critically read and finalized the manuscript.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

ETHICAL APPROVAL

No ethics approval was needed for this review.

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